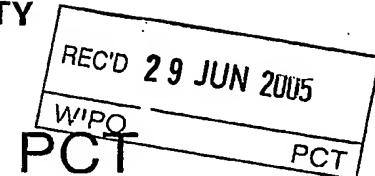


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

15 | 8

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

| | | |
|--|--|---|
| | | Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) |
| Applicant's or agent's file reference see form PCT/ISA/220 | | FOR FURTHER ACTION See paragraph 2 below |
| International application No. PCT/N2005/000010 | International filing date (day/month/year) 07.01.2005 | Priority date (day/month/year) 09.01.2004 |
| International Patent Classification (IPC) or both national classification and IPC C07D401/12, C07D409/14, C07D405/14, A61K31/4709, A61K31/4025, A61P29/00 | | |
| Applicant CADILA HEALTHCARE LIMITED | | |

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| | | |
|--|--|---|
| Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Kollmannsberger, M Telephone No. +49 89 2399-7364 |  |
|--|--|---|

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/N2005/000010

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. **type of material:**
 - a sequence listing
 - table(s) related to the sequence listing
 - b. **format of material:**
 - in written format
 - in computer readable form
 - c. **time of filing/furnishing:**
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 7,8

because:

the said international application, or the said claims Nos. 7,8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos.
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished

does not comply with the standard

the computer readable form

has not been furnished

does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IN2005/000010

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|-------------------------------|-------------|----------|
| Novelty (N) | Yes: Claims | 4 |
| | No: Claims | 1-3,5-11 |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-11 |
| Industrial applicability (IA) | Yes: Claims | 1-6,9-11 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/IN2005/000010

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 7 and 8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. Prior art

The following documents are considered relevant:

- D1: US-A-6 057 336 (DUAN ET AL) 2 May 2000 (2000-05-02)
- D2: US-B1-6 403 632 (DUAN JINGWU ET AL) 11 June 2002 (2002-06-11)
- D3: WO 02/04416 A (DUPONT PHARMACEUTICALS COMPANY) 17 January 2002 (2002-01-17)
- D4: WO 03/082287 A (BRISTOL-MYERS SQUIBB COMPANY; BENEDEK, IRMA, H; FOSSLER, MICHAEL, J) 9 October 2003 (2003-10-09)
- D5: DUAN JAMES J-W ET AL: "Discovery of gamma-lactam hydroxamic acids as selective inhibitors of tumor necrosis factor alpha converting enzyme: design, synthesis, and structure-activity relationships." JOURNAL OF MEDICINAL CHEMISTRY. 7 NOV 2002, vol. 45, no. 23, 7 November 2002 (2002-11-07), pages 4954-4957, XP002332807 ISSN: 0022-2623
- D6: WASSERMAN ZELDA R ET AL: "Identification of a selectivity determinant for inhibition of tumor necrosis factor-alpha converting enzyme by comparative modeling." CHEMISTRY & BIOLOGY. MAR 2003, vol. 10, no. 3, March 2003 (2003-03), pages 215-223, XP002332808 ISSN: 1074-5521

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/IN2005/000010

V-2. Novelty (Art. 33(2) PCT)

D1-D6 disclose TNF-alpha and/or MMP inhibitors included in the present claims (see passages indicated in the search report) as well as methods for their synthesis. Claims 1-3, 5-11 are thus not novel.

Claim 4 is novel since the compounds of claim 4 are not specifically disclosed in the cited documents.

V-3. Inventive step (Art. 33(3) PCT)

Claims 1-3, 5-11 are not novel and thus also not inventive.

The compounds of claim 4 are included in the general teachings of D1-D3 (see generic structures there) and differ only marginally from the example compounds disclosed therein (see e. g. D1, col. 205 examples 67-75). These compounds are thus considered to represent an obvious solution to the problem of finding further compounds having TNF and/or MMP inhibiting properties. Claim 4 does not fulfil Art. 33(3) PCT).